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Interventional Cardiology

Early Angiography Versus Conservative Treatment in Patients With Non–ST Elevation Acute Myocardial Infarction

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OBJECTIVES To compare short- and long-term outcome after early invasive or conservative strategies in the treatment of non-ST segment elevation acute myocardial infarction (AMI).

BACKGROUND It is uncertain whether or not there is benefit from emergent invasive diagnosis and treatment of AMI in patients without ST segment elevation on the admission electrocardiogram (ECG).

METHODS In a cohort of 1,635 consecutive patients with AMI who presented to hospitals without ST segment elevation on their admission ECG, we compared treatments, hospital course and outcome in 308 patients who presented to hospitals whose initial strategy favored early angiography and appropriate intervention when indicated versus 1,327 similar patients who presented to hospitals that favor a more conservative initial approach.

RESULTS At baseline, patients admitted to hospitals favoring an early invasive strategy were younger, more predominately Caucasian and had less comorbidity. Early coronary angiography occurred in 58.8% versus 8% ($p < 0.001$), and early angioplasty was performed in 44.8% versus 6.1% ($p < 0.001$) in the two different cohorts. Patients treated in hospitals favoring the early invasive strategy had a lower 30-day (5.5% vs. 9.5%, $p = 0.026$) and four-year mortality (20% vs. 37%, $p < 0.001$). Multivariate analysis showed a trend towards lower hospital mortality (OR = 0.56, 95% CI: 0.29 to 1.09) and a significant lower long-term mortality (hazard ratio = 0.61, 95% CI: 0.47 to 0.80) in patients admitted to hospitals favoring an early invasive strategy.

CONCLUSIONS These data suggested that an early invasive strategy in patients with AMI and nondiagnostic ECG changes is associated with lower long-term mortality. (J Am Coll Cardiol 2000;35: 895–902) © 2000 by the American College of Cardiology

Patients who present to the hospital with symptoms consistent with acute myocardial infarction (AMI) but have a nondiagnostic electrocardiogram represent a clinical challenge. Whereas patients who present with ST segment elevation are readily identified and can be treated with acute reperfusion therapy, those with AMI and nondiagnostic electrocardiograms (ECGs) are more difficult to diagnose at the time of admission and have not been shown to benefit from thrombolysis (1). Although hospital mortality is somewhat lower in patients who present with nondiagnostic ECG changes than in patients with ST segment elevation, long-term rates of reinfarction and mortality are similar (2).

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Acute angiography and reperfusion by coronary angioplasty or bypass surgery has been shown to result in improved outcomes in patients with AMI who present with ST segment elevation (3). However, in the setting of AMI without ST elevation, the value of acute intervention is less certain (1,4–7). The Thrombolysis in Myocardial Infarction (TIMI) IIIB trial (1,6) showed no benefit from a strategy

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of early invasive coronary angiography with target vessel revascularization, and the recent Veterans Affairs Non-Q Wave Infarction Strategies in Hospital (VANQWISH) trial showed worse outcome in these patients (4). However, Lotan et al. (5) showed improved short-term outcome in anterior wall AMI patients without ST segment elevation who were treated with an initial early invasive approach. None of these studies evaluated very early (<6 h) revascularization at the time of admission, and there is little data on

Abbreviations and Acronyms

ACEI	= angiotensin converting enzyme inhibitor
AMI	= acute myocardial infarction
CHARS	= Washington State Comprehensive Hospital Abstract Reporting System
ECG	= electrocardiogram
MITI	= Myocardial Infarction Triage and Intervention
SES	= socioeconomic status
TIMI	= Thrombolysis in Myocardial Infarction
VANQWISH	= Veterans Affairs Non-Q Wave Infarction Strategies in Hospital

outcome beyond one year. Thus, there is no consensus as to the efficacy of an early invasive strategy in this high risk patient group.

The Myocardial Infarction Triage and Intervention (MITI) Registry contains detailed data on a cohort of 12,331 consecutive patients with AMI. Because there was substantial variation in the process of care among the 19 hospitals in the registry, the initial approach to treatment of patients was more often determined by where patients were admitted than by characteristics of the patients themselves. Some Seattle-area hospitals favored an early diagnostic and intervention strategy in patients with suspected non-ST segment elevation AMI, while other hospitals favored a much more conservative initial strategy. We were, thus, able to perform an observational study comparing the influence of early invasive strategies on short- and long-term patient outcome.

METHODS

The subjects of this study were selected from a population of 12,331 consecutive patients with AMI who were enrolled in the MITI Registry between 1988 and 1994. Characteristics of the Registry, data-gathering procedures and reliability have been previously described (8). The MITI Trial and Registry was a collaborative effort to evaluate new treatment strategies for patients with AMI. The University of Washington Human Subjects Review Committee approved the study.

We performed a retrospective cohort analysis. The study cohort included 1,635 patients from the MITI Registry who had a confirmed AMI during their index hospitalization (based on a peak serum CPK/CPK-MB >/= 2× normal) but showed no ST segment elevation on their admission 12-lead ECG. Patients with evidence of cardiogenic shock at the time of admission were excluded. This cohort was divided into two groups: those patients initially admitted to hospitals that favored an early invasive strategy versus those that favored an initial conservative medical strategy. Hospitals favoring an early invasive strategy were defined as those hospitals that performed cardiac catheterization within 6 h of admission on 25% or more of patients with chest pain and nondiagnostic ECG changes. There were 308 patients included in the early invasive group admitted to two hospitals and 1,327 patients included in the conservative group admitted to the 17 remaining hospitals that favored a more conservative initial strategy. Eight of the 17 hospitals favoring a conservative initial strategy had on-site cardiac catheterization facilities.

Data collected. Trained abstractors collected detailed data on the patients' demographic characteristics, clinical presentation, hospital course and procedures within 3 months after discharge. Socioeconomic status (SES) was obtained by linking the registry to U.S. census data that assigns averages of education and income based on the address of the Registry patient. Readmissions and the rates of subsequent use of procedures were obtained by linking the MITI Registry to the Washington State Comprehensive Hospital Abstract Reporting System (CHARS). The CHARS database includes vital status for every hospital admission in the state of Washington. The rates of readmission and use of cardiac procedures were calculated at one and three years and are cumulative. The cardiac procedure use rate after discharge did not include procedures performed during the index admission.

Statistical analysis. Chi-square test, ANOVA and Student *t* tests were used to test for significant differences in baseline characteristics between patients in the early invasive and conservative cohorts. The rates of cardiac procedure use after discharge were compared at one and three years, and long-term mortality was compared with Kaplan-Meier plots and the log-rank test. To test whether there was an association between early invasive use of coronary angiography in suspected non-ST elevation AMI and hospital mortality independent of baseline differences, we constructed a series of logistic regression models. Factors associated with mortality in univariate comparisons were entered into the model in a step-wise fashion with type of admitting hospital (early invasive vs. conservative) forced into the model in the final step. The multivariate association between type of admitting hospital and long-term mortality was performed in a similar fashion using Cox regression models.

RESULTS

Baseline characteristics. Patients admitted to the hospitals favoring an early invasive strategy were younger (64 vs. 68 years, $p < 0.001$), more predominately Caucasian (98% vs. 91%, $p < 0.001$) and had higher SES on average (owner occupied housing 72% vs. 61%, $p < 0.001$, median household annual income $48,197 vs. $36,064, $p < 0.001$, college graduate 42.9% vs. 34.6%, $p < 0.001$). They had a lower prevalence of prior angina (37% vs. 48%, $p < 0.001$), past history of MI (20% vs. 30%, $p < 0.001$) and congestive heart failure (9% vs. 17%, $p < 0.001$). Electrocardiogram at

Table 1. Baseline Characteristics of Patients With AMI and Nondiagnostic ECG Changes Admitted to Conservative Hospitals Versus Hospitals Favoring an Early Invasive Strategy*

	Conservative (n = 1,327)	Early Invasive (n = 412)	p Value
Age, yr (mean ± standard deviation)	68 ± 12.7	64 ± 12.2	< 0.001
Gender (% male)	66	70	0.149
Race (% white)	91	98	< 0.001
SES			
Owner-occupied housing	61	72	< 0.001
Median household income	$36,064	$48,197	< 0.001
College graduate	34	42	< 0.001
Professional, executive, manager	20	26	< 0.001
Prior history			
Angina	48	36	< 0.001
Hypertension	50	51	0.726
Myocardial infarction	30	20	< 0.001
Congestive heart failure	17	9	< 0.001
Cardiac surgery	12	15	0.257
Diabetes	21	16	0.093
Smoking cigarettes	32	27	0.082
ECG findings			
ST segment depression	44.3%	36.2%	0.012
T wave inversion	25.0%	26.9%	0.510
Other ECG findings	30.7%	36.9%	0.091

*Conservative and early invasive hospitals as defined in "Methods" section.

presentation varied between cohorts; there were modest differences in the proportion of patients presenting with ST segment depression (36% vs. 44%, p = 0.01 in early invasive and conservative hospitals, respectively), T wave inversion (25% vs. 27%, p = 0.51) or "other" ECG findings (31% vs. 37%, p = 0.09). There were no significant differences in gender, past history of hypertension, cardiac surgery, diabetes or cigarette smoking (Table 1). There was no difference in mean peak CPK values between the two groups (1,133 ± 1,506 vs. 1,042 ± 1,069, p = 0.36).

Hospital procedure use and short-term outcome. As expected, patients admitted to hospitals favoring an early invasive strategy were more likely to undergo cardiac catheterization during their index hospitalization than patients admitted to hospitals favoring a conservative initial strategy (86% vs. 52%, p < 0.001). Patients admitted to hospitals favoring an early invasive strategy were also more likely to undergo cardiac catheterization within 6 h of presenting to the emergency department (59% vs. 8%, p < 0.001). They were also more likely to undergo angioplasty during their index hospitalization (60% vs. 22%, p < 0.001) and within 6 h of admission (45% vs. 6%, p < 0.001). Coronary artery bypass graft surgery was performed more often in patients admitted to early invasive hospitals (20% vs. 13%, p = 0.001) (Fig. 1). The types of cardiac medications prescribed at discharge were similar between the two cohorts. However, patients at hospitals favoring an early invasive strategy were more likely to be discharged with aspirin (71% vs. 63%, p = 0.018) and less likely to be discharged with beta-adrenergic blocking agents (17% vs. 27%, p < 0.001). There was no gender difference for patients who underwent coronary angiography during hospitalization between the early invasive and conservative cohorts (73% vs. 74% male gender, p = 0.789). There was also no difference in the proportion of men undergoing angiography within 6 h of admission between the two cohorts (75% vs. 82%, p = 0.11).

Patients admitted to hospitals favoring an early invasive strategy were less likely to develop evidence of new congestive heart failure during their index hospitalization than patients admitted to hospitals favoring a conservative initial strategy (24% vs. 35%, p = 0.001). There was no significant difference in the rate of stroke between the two groups. Unadjusted 30-day mortality was lower in patients admitted to hospitals favoring an early invasive strategy (5.5% vs. 9.5%, p = 0.026), and there was a trend in this group toward decreased recurrent AMI (2.3% vs. 3.5%, p = 0.287) (Fig. 2). In order to evaluate the association between the type of admitting hospital (early invasive vs. conservative) and hospital mortality independent of differences in baseline characteristics, we performed a series of logistic regression models. Factors associated with higher hospital mortality included increased age, in-hospital extension of MI, in-hospital stroke and new-onset heart failure. There was a nonsignificant association between admission to an early invasive hospital and lower mortality (OR = 0.56, 95% CI: 0.25 to 1.21) (Fig. 3).

To further examine the outcome effect of early invasive angiography, we performed a subgroup analysis of only those patients admitted to hospitals favoring an early

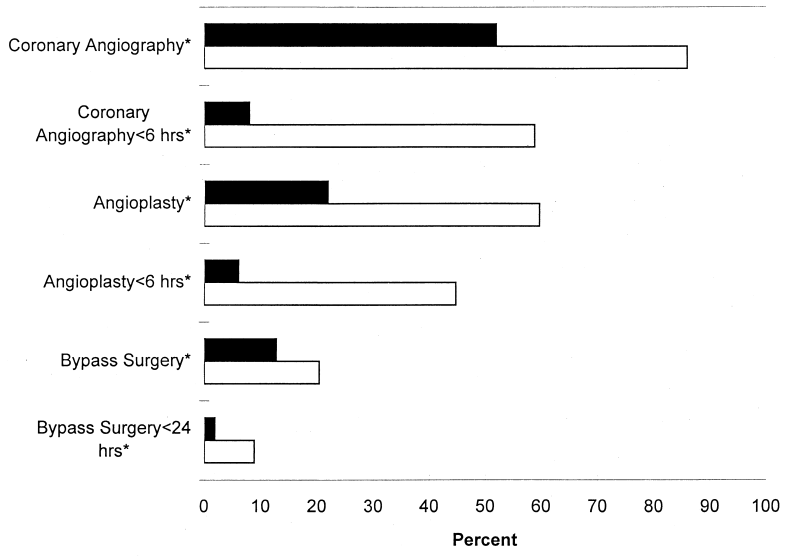

Figure 1. In-hospital procedures performed at conservative hospitals versus hospitals favoring an early invasive strategy. Patients admitted to hospitals favoring an early invasive strategy were more likely to undergo coronary angiography, coronary angioplasty and coronary artery bypass grafting during their index hospitalization, as well as coronary angiography and coronary angioplasty within 6 h of admission and coronary artery bypass grafting within 24 h of admission. *$p < 0.05$. **Closed bar** = conservative; **open bar** = early invasive.

invasive strategy. We compared in-hospital mortality of patients who received coronary angiography within 6 h of admission to those who did not. We found that patients who received early invasive coronary angiography had significantly lower in-hospital mortality than those who did not (1.1% vs. 7.1%, $p = 0.005$). After adjustment for differences in patients who did versus those who did not receive early angiography, there was a nonsignificant trend between early angiography and lower hospital mortality (OR = 0.29 95%, CI = 0.06 to 1.4).

Long-term outcome. Patients were followed for a mean of 3.2 years. After hospital discharge, patients admitted to hospitals favoring an early invasive strategy were more likely to undergo subsequent cardiac catheterization (23% vs. 16%, $p = 0.012$ at three years) (Fig. 4). There were no differences between the groups in the rate of cardiac-related rehospitalizations, coronary angioplasty or bypass surgery at one and three year follow-up.

Patients admitted to hospitals favoring an early invasive strategy had better long-term survival than those admitted

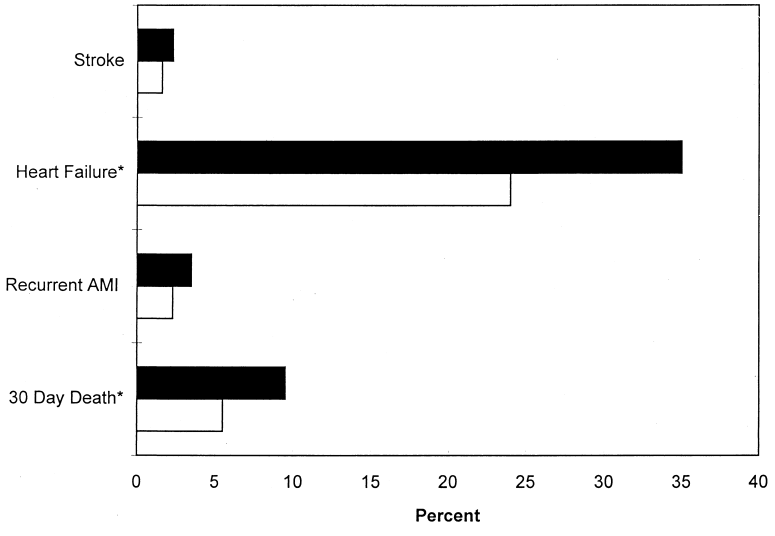

Figure 2. Hospital events at conservative hospitals versus hospitals favoring an early invasive strategy. More patients admitted to hospitals favoring a conservative initial strategy developed congestive heart failure during their index hospitalization. Additionally, 30-day mortality was higher at hospitals favoring a conservative initial strategy. MI = myocardial infarction; 30 day death = death within 30 days of index admission. *$p < 0.05$. **Closed bar** = conservative; **open bar** = early invasive.

Figure 3. Factors associated with a higher risk of death during the index hospitalization in patients admitted to early invasive and hospitals favoring a conservative initial strategy. Odds ratios to the right of the line of identity (odds ratio, 1) are associated with a higher risk of in-hospital mortality. After adjustment for all measured factors that predict mortality, there was a nonsignificant association between admission to hospitals favoring an early invasive strategy and reduced in-hospital mortality (OR = 0.56, 95% CI, 0.29 to 1.093).

to hospitals favoring a conservative initial strategy (81% vs. 63% at four years, $p < 0.001$) (Fig. 5). This survival advantage was greatest in a subpopulation of patients presenting with ST depression (75% vs. 53% at four years, $p < 0.001$).

To investigate the association between type of admitting hospital (early invasive vs. conservative) and long-term mortality independent of differences in the baseline characteristics of cohorts, we performed multivariate Cox analyses. Factors associated with increased long-term mortality included older age, employment in a "blue collar" occupation, heart failure during the hospitalization, stroke, prior heart failure and prior myocardial infarction (Fig. 6). Factors associated with lower long-term mortality included discharge medications of either ASA or beta-blockers. After adjustment for these factors, there was a significant association between admission to hospitals favoring an early invasive strategy and lower long-term mortality (hazard ratio = 0.63, 95% CI: 0.47 to 0.83).

We further validated our results by evaluating a subgroup of 708 patients less than or equal to 65 years of age (173 admitted to early invasive hospitals and 535 admitted to more conservative hospitals). This subgroup was better matched in terms of age (55.2 ± 6.7 vs. 54.9 ± 7.6 years,

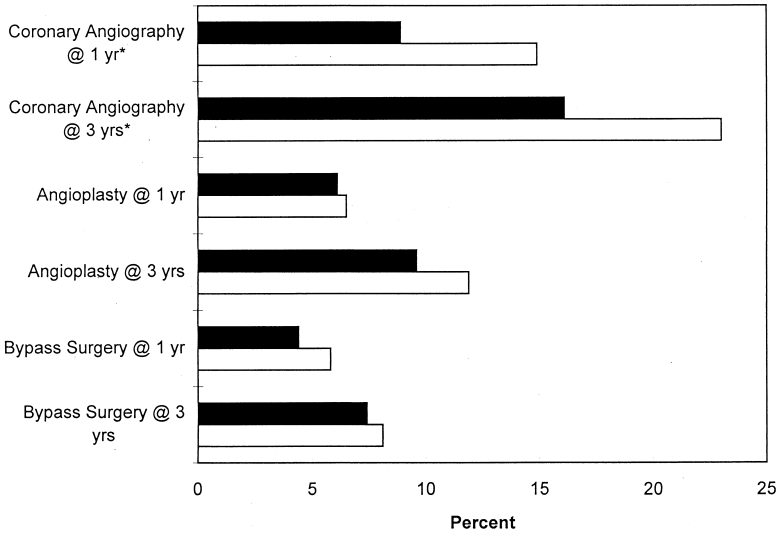

Figure 4. Procedures after discharge at conservative hospitals versus hospitals favoring an early invasive strategy. Patients treated at hospitals favoring an early invasive strategy were more likely to undergo repeat coronary angiography by one and three years. There was no difference in the rate of coronary angioplasty or coronary artery bypass grafting by one or three years. *$p < 0.05$. **Closed bar** = conservative; **open bar** = early invasive.

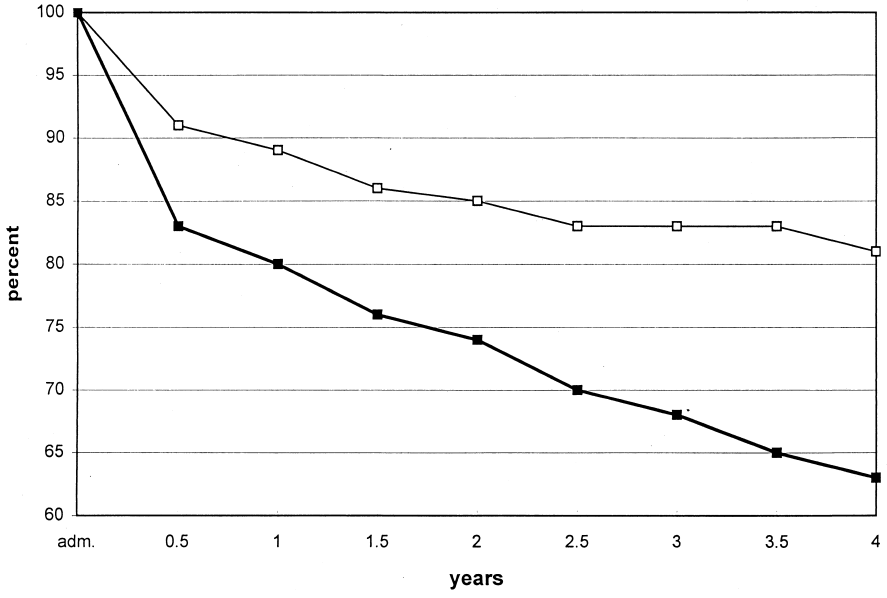

Figure 5. Survival rates during follow-up in patients admitted to early invasive and hospitals favoring a conservative initial strategy. In this unadjusted comparison, patients treated at hospitals favoring an early invasive strategy had improved long-term survival (81% vs. 63% at four years, $p < 0.001$, mean follow-up 3.2 years). **Closed square** = conservative; **open square** = early invasive.

$p = 0.64$ in early invasive vs. conservative patients, respectively) and gender (17.9% vs. 22.1% female, $p = 0.146$). Past history was similar except for a lower proportion of past heart failure in patients admitted to early invasive hospitals (4.0% vs. 8.6%, $p = 0.05$). Mortality at hospital discharge and at four years follow-up was lower in patients admitted to early invasive hospitals (0% vs. 3.2%, $p = 0.008$ at hospital discharge and 12.9% vs. 19.7%, $p = 0.078$ at four years follow-up). After multivariate adjustment for differences in baseline characteristics in this subgroup of patients, there was a nonsignificant association between admission to an early invasive hospital and lower long-term mortality (hazard ratio = 0.65, 95% CI = 0.38 to 1.13).

DISCUSSION

One of the reasons for the declining mortality rate in patients with AMI is the rapid diagnosis and treatment of patients presenting with ST segment elevation (9). For patients without ST segment elevation on their admission 12-lead ECG, evidence for rapid identification and treatment has been less convincing (3–6). The use of thrombo-

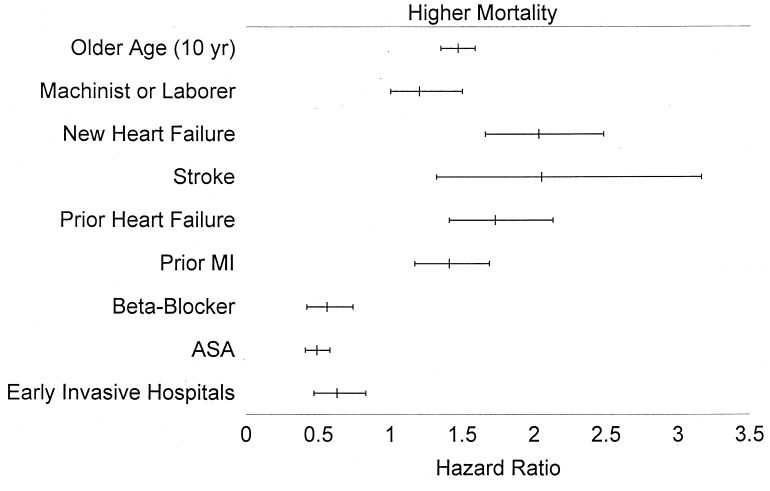

Figure 6. Factors associated with higher risk of death during follow-up in patients admitted to early invasive and hospitals favoring a conservative initial strategy. Hazard ratios to the right of the line of identity (hazard ratio, 1) are associated with a higher risk of long-term mortality. After adjustment for all measured factors that predict mortality, admission to hospitals favoring an early invasive strategy was independently associated with decreased long-term mortality (hazard ratio 0.61, 95% CI, 0.47 to 0.80).

lytic therapy in this patient group has resulted in less favorable outcomes (1). Several therapies, such as the use of aspirin (10), beta-blockers (11) and angiotensin converting enzyme inhibitors (ACEI) (12) have been shown to reduce mortality in patients with AMI and non–ST segment elevation on the admission ECG. However, no therapies have been identified in this patient group that, when delivered early, could lead to attenuation of myocardial cell death.

The early use of coronary angiography and revascularization, if needed, holds theoretical promise for identification and treatment of high-risk infarct patients. We evaluated data from the MITI Registry in 1,635 AMI patients to see if admission to hospitals that favor early angiography and revascularization in these patients was associated with improved short-term or long-term outcomes.

Findings. In this observational study, we found that patients admitted to hospitals favoring an early invasive strategy were far more likely to undergo cardiac procedures both emergently (<6 h) and electively. This treatment strategy was associated with lower rates of heart failure during the index hospitalization and lower 30-day mortality. Indeed, after a mean of 3.2 years of follow-up, patients admitted to hospitals favoring an early invasive strategy had lower mortality in comparison with those admitted to hospitals favoring a conservative initial strategy. Multivariate analysis showed that admission to hospitals favoring an early invasive strategy was an independent predictor of decreased long-term mortality. This observed lower mortality in the early invasive cohort may have been a function of either earlier revascularization and associated improved myocardial salvage or simply more revascularization than those patients admitted to hospitals favoring a conservative initial strategy. However, the remarkably low mortality observed in our subgroup analysis of patients admitted to hospitals favoring an early invasive strategy who actually underwent angiography within 6 h of admission (1.1% vs. 7.1%, $p = 0.005$ in hospital, 10% vs. 32.5%, $p < 0.001$ at four years post-index event) argues that myocardial salvage may play an important role.

Previous studies. These findings differ from previous studies evaluating early invasive therapy in non-ST elevation AMI patients. In the TIMI IIIB randomized trial (1), there was no mortality benefit in patients with non-Q wave AMI or unstable angina randomized to an early invasive strategy (arteriography with revascularization if indicated). In this trial, early invasive angiography was designed to be performed 18 to 48 h after randomization, and patients randomized to early invasive therapy were treated relatively late after hospital admission (mean 36 h). After such a delay, there may be less myocardial salvage and, therefore, less benefit from revascularization. In addition, the TIMI IIIB study consisted predominately of patients with unstable angina in whom the risk of death is less than for AMI.

More recently, the results of the VANQWISH trial were reported (4). In this trial, patients with non–Q Wave AMI were randomized to either catheterization and revascularization (invasive strategy) or a more conservative approach, with catheterization and revascularization reserved only for patients with either rest or inducible ischemia before discharge. In this trial, patients randomized to the invasive strategy had higher mortality and more cardiac events than the conservative strategy in-hospital and up to 12 months after randomization but showed no significant difference in outcome at 23 months. The VANQWISH trial differed from the MITI study in that catheterizations in the VANQWISH trial were performed electively after admission, with a mean time from randomization to revascularization of eight days in the invasive strategy group. This delay in revascularization could account for the difference in results between VANQWISH and our study. Early angiography was performed earlier in the Medicine Versus Angiography in Thrombolytic Exclusion trial (mean time 27 h); however, there still was no observed difference in outcome in patients randomized to a strategy of early catheterization and intervention (7).

In contrast to those trials, the recently reported Fast Revascularization during Instability in Coronary Disease study (FRISC II) showed a 21% reduction in death or MI in patients randomized to early angiography (2 to 7 days) versus a more conservative ischemia-driven strategy (13). Lotan et al. (5) also observed improved outcomes with an early invasive strategy in a study of 110 patients with non-Q wave AMI. In this study, patients with non–Q wave anterior wall AMIs were retrospectively evaluated by whether or not they received early invasive therapy. Lotan found that patients treated with an early invasive strategy had fewer recurrent AMIs, decreased angina pectoris, less congestive heart failure and improved long-term survival at three years. The patients in Lotan's study were assigned to cohorts based on treatment, unlike our study in which patients were assigned to cohorts based on their admission hospitals.

Implications. Taken together, these studies imply that there may be a benefit of early catheterization without prior noninvasive testing in select patients after non-ST segment elevation MI. The conflicting results are more likely a result of patient selection and choice of revascularization protocols in the trials. What is less clear is the value of early catheterization (within 6 h of admission) as was evaluated in the present MITI Registry study. Although we found an association between early catheterization and improved outcome, our findings should be confirmed in a randomized trial.

Study limitations. Although our findings are provocative, there are limitations inherent in a retrospective cohort analysis. Because neither the admitting hospital nor treatments received were randomly assigned, there could be selection bias in our analyses. We attempted to control bias by performing analyses based on the admitting hospital

rather than by the treatments a patient had received. This resulted in some balance between cohorts. However, patients admitted to hospitals favoring an early invasive strategy were, in fact, younger, had higher SES and had less comorbidity. Although we could adjust for these measured factors by performing multivariate analyses, we could not adjust for unmeasured differences between cohorts. Unlike many other registry studies, however, in the MITI Registry, we were able to account for patient transfer, measure and adjust for differences in SES and obtain accurate long-term follow-up. These advantages minimize, but do not eliminate, the selection bias inherent in observational studies.

Conclusions. We conclude that admission to a hospital that favors a strategy of early coronary angiography and revascularization is associated with lower long-term mortality in select patients presenting with nonspecific findings on admission ECG. Our data support performing a randomized trial to evaluate an early invasive strategy in the treatment of patients who present with symptoms of AMI but without ST segment elevation on their admission ECG.

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